*Kidney International, Vol. 65 (2004), pp. 990–998*

CLINICAL NEPHROLOGY – EPIDEMIOLOGY – CLINICAL TRIALS

# Willingness of dialysis patients to participate in a randomized controlled trial of daily dialysis

**AJAY K. ISRANI, SCOTT D. HALPERN, CHRISTOPHER MCFADDEN, RUBEEN K. ISRANI, ALAN WASSERSTEIN, SIDNEY KOBRIN, and JEFFREY S. BERNS**

*Renal-Electrolyte & Hypertension Division, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania*

**Willingness of dialysis patients to participate in a randomized controlled trial of daily dialysis.**

*Background.* The National Institutes of Health (NIH) has proposed conducting randomized controlled trials comparing short, daily, in-center hemodialysis with conventional hemodialysis. However, there is concern that difficulties recruiting patients may prevent the successful completion of such trials if patients believe the inconveniences of daily dialysis outweigh any potential health benefits.

*Methods.* To gauge willingness to participate in a daily dialysis trial, we described a hypothetical, randomized controlled trial comparing conventional to daily hemodialysis to 209 chronic hemodialysis patients, and assessed their motivations for and concerns about participating.

*Results.* We found that 85 patients (41%) of 209 patients who agreed to be interviewed expressed some willingness to participate in the hypothetical trial. Patients who expressed greater willingness to participate were younger (OR for participating = 0.96 per year, 95% CI = 0.94 to 0.98, $P = 0.001$), less likely to smoke (OR = 0.38, 95% CI = 0.17 to 0.84, $P = 0.017$), more likely to have been hospitalized during the last 12 months (OR = 2.8, 95% CI = 1.5 to 5.5, $P = 0.002$), less likely to have reactive airway disease (OR = 0.21, 95% CI = 0.06 to 0.69, $P = 0.01$) or coronary artery disease (OR = 0.20, 95% CI = 0.08 to 0.53, $P = 0.001$), and less likely to be on the waiting list for a kidney transplant (OR = 0.23, 95% CI = 0.10 to 0.50, $P < 0.0001$).

*Conclusion.* The study suggests that less than half of eligible patients would be willing to participate in the randomized controlled trial. Differing willingness to participate across patient subgroups suggests that certain subgroups (i.e., older patients and those with coronary artery disease) will need to be targeted to ensure that results are generalizable to most hemodialysis patients.

Long-term hemodialysis has been recognized as a life-saving intervention since the 1970s. A three-times-per-week regimen has been the standard of care for most hemodialysis patients. However, this regimen has been based primarily on practical considerations of transportation and scheduling a rapidly growing number of end-stage renal disease (ESRD) patients requiring chronic dialysis rather than demonstrated superiority to other regimens [1, 2]. Recently, case series conducted in the United States, Canada, and Europe have highlighted the putative advantages of short, daily hemodialysis (in-center treatments six times each week) [abstracts; Ting et al, *Perit Dial Int* 18:S78A, 1998; Ting et al, *J Am Soc Nephrol* 9:228A, 1998; Ting et al, *J Am Soc Nephrol* 9:228A, 1998; Buoncristiani et al, *J Am Soc Nephrol* 8: 216A, 1997; Buoncristiani, *J Am Soc Nephrol* 8:216A, 1997] [3–8]. Despite these reported advantages of daily dialysis, the absence of randomized controlled trials comparing conventional to daily dialysis prevents robust conclusions regarding which is to be preferred. To improve decision-making for the approximately 300,000 patients requiring long-term dialysis in the United States [9], the National Institutes of Health (NIH) has proposed funding for randomized controlled trials of daily hemodialysis in which dialysis patients would be randomly assigned to receive daily hemodialysis (six times a week) or conventional hemodialysis (three times a week) [10, 11].

A major barrier to the successful conduct of randomized controlled trials is the difficulty recruiting eligible patients [12–16]. Recruitment may be particularly difficult for the proposed randomized controlled trials of daily hemodialysis because patients may view the inconvenience of daily dialysis to outweigh any potential health benefits of daily dialysis. Therefore the proposed trials may experience underenrollment—the enrollment of too few subjects to obtain adequate statistical power to reliably detect an effect—and selective enrollment—the disproportionate enrollment of certain patient subgroups (e.g., those with relatively few comorbid illnesses). These phenomena would threaten the precision and generalizability of the results, respectively [13].

**Key words:** daily dialysis, randomized controlled clinical trials, willingness to participate.

Received for publication April 15, 2003
and in revised form July 1, 2003, and September 15, 2003
Accepted for publication October 1, 2003

One method to help overcome these problems is to prospectively assess potential research participants' preferences for trial enrollment. Prospective preference assessment may enhance the subsequent trial's scientific value in several ways [13]. First, identifying patients for whom research participation is consistent with their interests and values may enhance the efficiency of participant accrual by guiding recruitment efforts toward those most likely to agree to enroll. Second, prospectively assessing willingness to participate among members of the target population may provide insight into the generalizability of the results. Third, identifying individuals with sincere interests in participating may help investigators enroll patients who are more likely to adhere to study protocols [17], reducing the potential for bias due to post-randomization losses [18].

To help guide the conduct of proposed randomized controlled trials of daily hemodialysis, we prospectively assessed dialysis patients' stated willingness to participate in a hypothetical trial that mimicked those likely to be initiated through support from the NIH [19]. We had three primary goals. Our first goal was to gauge the likelihood for successful enrollment in actual randomized controlled trials once initiated. Second, we aimed to determine ESRD patients' motivations for and concerns about participating in such a trial so as to guide the design and conduct of future randomized controlled trials. Finally, we sought to evaluate differences in demographic and disease-related characteristics among those who are and are not likely to enroll in actual trials so as to anticipate the generalizability of the results from future randomized controlled trials. Our secondary aim was to determine the effect of formalized teaching about the risks and benefits of daily dialysis on patients' stated willingness to participate in the proposed trial.

## METHODS

### Patients

Between July 2002 and December 2002, we enrolled patients receiving chronic hemodialysis at the three dialysis units affiliated with the University of Pennsylvania Medical Center. Two of the dialysis units were urban and the third one was a suburban unit. A total of 331 patients were receiving dialysis during this period. We aimed to include all patients except those who were unable to speak English or understand the consent form (e.g., due to dementia). Sixty-one patients (18%) refused to participate, 18 (5%) were unavailable for interview, and 18 (5%) met the foregoing exclusion criteria. The remaining 234 patients gave written, informed consent and were interviewed while on dialysis. None of the patients were offered a financial incentive for participating in our survey study. This study was approved by the University of Pennsylvania Institutional Review Board (Fig. 1).

### Study design

One of the four physician investigators not involved in the care of the dialysis patients at the time of the study interviewed each patient individually for approximately 15 minutes during one of their dialysis sessions. During the first part of the interview, the investigator read a scripted description of a 3-year, hypothetical, randomized controlled trial comparing conventional (three times weekly) hemodialysis with daily (2-hour treatments, six times weekly) dialysis (see Appendix 1). This hypothetical trial reflected the design features the investigators anticipate will be employed in an upcoming, actual randomized controlled trial of conventional versus daily dialysis. These design features were based on a NIH-sponsored conference on daily dialysis [19]. The investigator also reviewed the potential benefits of daily dialysis using a previously piloted script. Several small case series indicate that daily dialysis may improve several surrogate markers of health, such as blood pressure control, hematocrit, and serum albumin and prealbumin, as well as the true clinical end points of reduced symptoms such as cramping and headaches, and an overall improvement in quality of life [3, 6, 7, 20, 21]. There is hope, albeit limited evidence, that more frequent dialysis regimens might reduce hospitalizations, reduce use of erythropoietin and blood pressure medications, and extend life expectancy [8, 22]. The investigator also reviewed the potential risks of daily dialysis using a previously piloted script. These include the uncertain risks of vascular access failure associated with more frequent use. The investigator then asked the patient four previously scripted questions [13] to assess the patient's understanding of the described trial. These four questions assessed the patient's understanding of randomization, differences between the two arms of the trial and the duration of the trial (see Appendix 1). Any areas of misunderstanding were explained, and the patient was then requestioned. Twenty-five patients (8%) were excluded because they failed to demonstrate adequate understanding. Most of these excluded patients had a poor understanding of the concept of randomization.

The remaining 209 patients (Fig. 1) were asked open-ended questions about their motivations for, and concerns about participating in the hypothetical trial. The patients were encouraged to state as many motivating and concerning factors that were important to them. Their responses were transcribed and subsequently categorized. Next, the investigator asked patients to indicate their willingness to participate in the described trial (this represented the baseline willingness to participate) using a 6-point scale from "definitely not willing" to "definitely willing." Patients also completed a two-page form assessing demographic characteristics, disease-related characteristics, and comorbidities. Disease-related characteristics, including treatment variables, medications

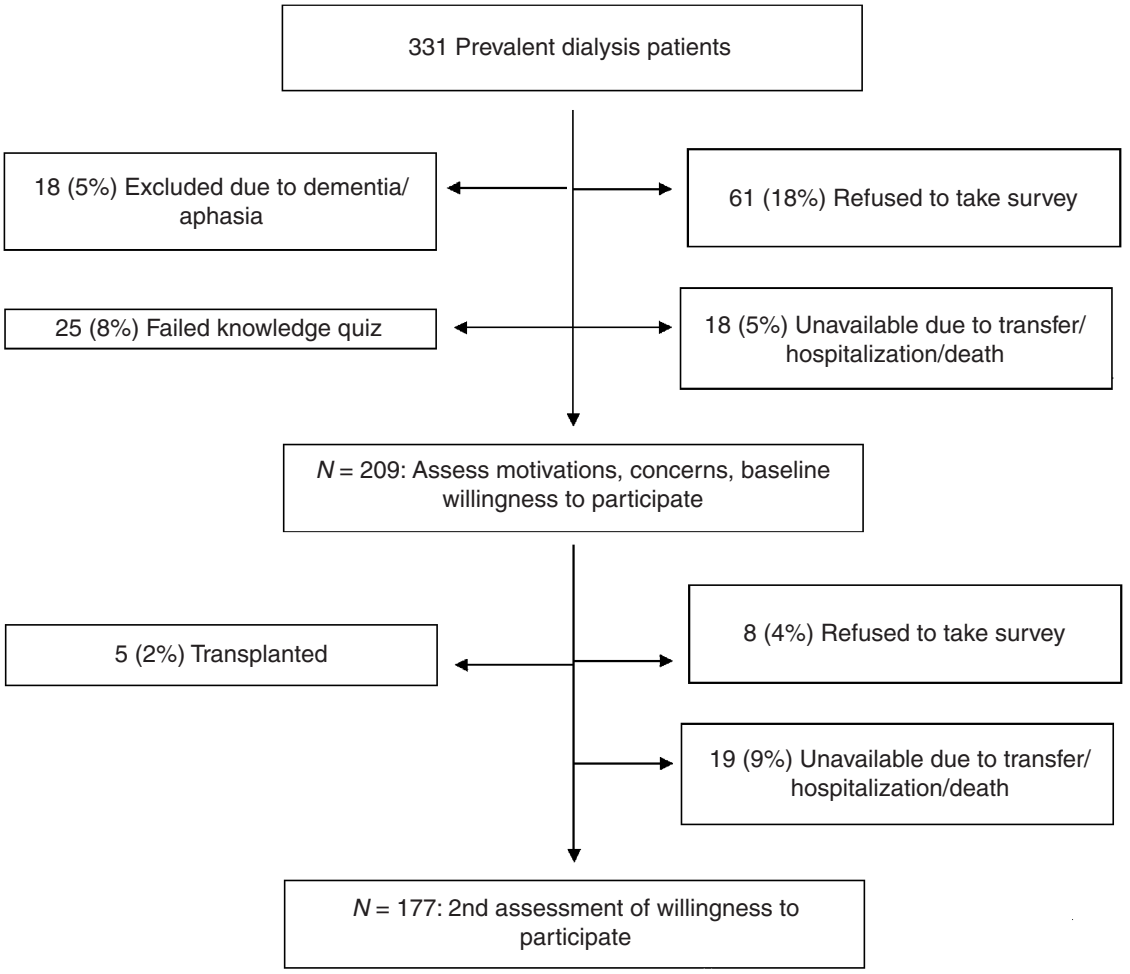


**Fig. 1. Patients participating in the first and second part of the survey.** For the baseline assessment of their willingess to participate, 122 (37%) of the 331 dialysis patients in our cohort study could not be surveyed. For the second assessment of their willingness to participate, 32 (15%) of the 209 patients could not be surveyed. At least three attempts were made over the 6 months of the study to capture all patients in the cohort.

currently being taken, and whether or not the patient had been listed for renal transplantation, were confirmed by abstracting data from the patients' medical records.

Approximately 1 month after their initial interview, patients were provided a one-on-one verbal teaching session that was scripted and led by one of the investigators during one of their dialysis treatments. This session again presented information in detail regarding the potential health benefits, risks, and inconveniences associated with the novel, daily dialysis regimen (see Appendix 2). Once patients had completed the formal teaching, investigators reassessed their willingness to participate using the same 6-point scale. Of the 209 patients who had participated in the first part of the survey, 32 (15%) were unable or unwilling to participate in this second assessment of their willingness to participate. The remaining 177 patients (85%) participated in the second interview. (Fig. 1)

## Statistical analysis

We used Student *t* tests to compare those willing to participate and those unwilling to participate with regard to normally distributed variables, and chi-squared tests for comparisons on categorical variables. We constructed both an ordinal logistic regression model (using stated willingness to participate as an ordinal variable) and a logistic regression model (using stated willingness to participate as a dichotomous variable) to evaluate the influence of the various patient characteristics (such as comorbid illnesses and demographic factors) on willingness to participate in the trial. We dichotomized willingness to participate a priori, by considering all patients who gave a positive response on the 6-point scale ("might, "probably," or "definitely" willing to participate) as willing to participate. Because the direction of effect of the coefficients for the attributes were similar in the dichotomous and the ordinal logistic regression models, we present only the results of the dichotomous model because this

**Table 1.** Characteristics of survey patients (number in parenthesis is percentage unless otherwise stated)

| | All patients | Not willing to participate | Willing to participate |
|---|---|---|---|
| | ($N = 209$) | ($N = 124$) | ($N = 85$) |
| Age *years* (± SD) | 56 ± 15 | 58 ± 14 | 52 ± 15[a] |
| Female | 106 (51%) | 66 (52%) | 40 (47%) |
| Race | | | |
| Non-Hispanic African Americans | 173 (83%) | 103 (83%) | 70 (82%) |
| Non-Hispanic white | 25 (12%) | 16 (13%) | 9 (11%) |
| Others | 11 (5%) | 5 (4%) | 6 (7%) |
| Years of education (± SD) | 12.7 (± 2.5) | 12.6 (±2.5) | 12.7 (±2.5) |
| Mean household income[b] | $15,001–30,000 | $15,001–30,000 | $15,001–30,000 |
| Employed | 30 (14%) | 15 (12%) | 15 (18%) |
| Mode of transportation | | | |
| Personal | 95 (45%) | 53 (43%) | 42 (49%) |
| Public | 27 (13%) | 17 (13%) | 10 (12%) |
| Institutional | 87 (42%) | 54 (44%) | 33 (39%) |
| Current smoker | 50 (24%) | 35 (28%) | 14 (17%) |
| Length of time on dialysis *years* | 4.0 ± 4 | 4.3 ± 4.2 | 3.6 ± 3.7 |
| Number of hospitalizations last year | 1.5 ± 2.4 | 1.1 ± 1.8 | 2.0 ± 3.0[a] |
| Transplant waiting-list status | | | |
| Evaluated for kidney transplantation | 111 (53%) | 71 (57%) | 40 (47%) |
| On list for kidney transplantation | 62 (30%) | 45 (36%) | 17 (20%)[a] |
| Stated quality of personal health | | | |
| Excellent | 6 (3%) | 5 (4%) | 1 (1%) |
| Very good | 30 (14%) | 18 (15%) | 12 (14%) |
| Good | 62 (30%) | 34 (27%) | 28 (33%) |
| Fair | 84 (40%) | 52 (42%) | 32 (38%) |
| Poor | 27 (13%) | 15 (12%) | 12 (14%) |
| Vascular access type | | | |
| Arteriovenous fistula | 72 (35%) | 45 (36%) | 27 (32%) |
| Arteriovenous grafts | 102 (50%) | 59 (49%) | 43 (51%) |
| Catheter | 32 (16%) | 18 (15%) | 14 (17%) |
| Average Kt/V for last 3 months | 1.47 (0.2) | 1.47 (± 0.2) | 1.46 (± 0.2) |
| Treatment time *hours per week* | 11.3 (1.7) | 11.1 (± 1.6) | 11.5 (± 1.7) |

[a] $P < 0.05$; [b] Fifteen patients did not give this information.

better reflects the decision that patients must ultimately make. We included in the multivariable model all variables reaching $P < 0.20$ in univariable analyses. We used McNemar's test to compare willingness to participate at baseline and after formal teaching. $P$ values <0.05 were considered statistically significant.

With 209 patients enrolled, and at an alpha level of 0.05, we had at least 80% power to detect differences of 20% in the proportions of patients who were willing to participate when patient subgroups were defined such that from 30% to 70% of patients had a particular comorbid condition.

## RESULTS

The characteristics of the 209 patients who completed the first interview are described in Table 1. Overall, the percentages of patients who said they "definitely would not," "probably would not," "maybe would not," "may be would," "probably would," and "definitely would" participate were 29%, 21%, 9%, 17%, 17%, and 7%, respectively. Thus, 85 of the 209 survey patients (41%) were considered willing to participate in a randomized controlled trial of short daily hemodialysis (Fig. 2).

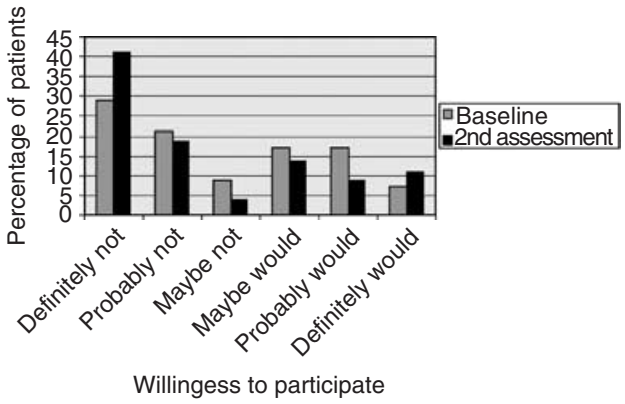


**Fig. 2. Response to question: How willing would you be to participate in this study of six versus three times a week dialysis?** At baseline among 209 patients, 85 (41%) stated a positive willingness to participate whereas 124 (59%) were not willing to participate. After teaching about the possible risks and benefits of daily dialysis, among 177 patients, 62 (35%) stated a positive willingness to participate whereas 115 (65%) were not willing to participate.

### Influence of demographic and disease-related characteristics on willingness to participate

Univariable analyses revealed that, compared with patients who were unwilling to participate, those who were

**Table 2.** Variables associated with willingness to participate: A univariate and multivariate analysis[a]

| Variable | Unadjusted OR (95% CI) | Unadjusted *P* value | Adjusted OR (95% CI) | Adjusted *P* value |
|---|---|---|---|---|
| Age per year | 0.97 (0.95–0.99) | 0.004 | 0.96 (0.94–0.98) | 0.001 |
| Hospitalization last year | 2.37 (1.3–4.2) | 0.003 | 2.8 (1.5–5.5) | 0.002 |
| Current smoker | 0.54 (0.28–1.08) | 0.081 | 0.38 (0.17–0.84) | 0.017 |
| Dialysis treatment time, per hour | 1.15 (0.97–1.36) | 0.113 | — | |
| On list for kidney transplant | 0.44 (0.23–0.84) | 0.012 | 0.23 (0.10–0.50) | <0.0001 |
| Evaluated for a kidney transplant | 0.66 (0.38–1.15) | 0.147 | — | |
| History of reactive airway disease | 0.32 (0.12–0.90) | 0.031 | 0.21 (0.06–0.69) | 0.011 |
| History of coronary artery disease | 0.22 (0.09–0.52) | 0.001 | 0.20 (0.08–0.53) | 0.001 |
| History of arrhythmia | 0.53 (0.30–0.96) | 0.035 | — | |
| History of coronary artery bypass grafting | 0.25 (0.05–1.15) | 0.074 | — | |
| History of coronary angioplasty | 0.25 (0.7–0.88) | 0.030 | — | |

[a]Variables that were not significantly associated with willingness to participate by univariate anlaysis include gender, race, years of education, mean household income, employment status, mode of transportation, dialysis unit, location of dialysis unit (suburban versus urban location), interviewer, length of time on dialysis in years, stated quality of personal health, type of vascular access, and disease-related factors such as albumin, calcium-phosphorus product, Kt/V, number of medications for hypertension, and number of phosphate binders.

willing to participate were younger, nonsmokers, and more likely to have been hospitalized in the preceding 12 months, and not on the waiting list for a renal transplant. Patients who were willing to participate were also less likely to have a history of reactive airway disease (asthma or emphysema), arrhythmias, coronary artery disease, or a coronary angioplasty (Table 2). Several of these differences remained significant after adjustment for confounding in multivariable analysis (Table 2). In the multivariable model, we found that patients who were willing to participate in the randomized controlled trial were younger, nonsmokers, and more likely to be hospitalized in the preceding 12 months. They were also less likely to be on the waiting list for a kidney transplant and less likely to have a history of reactive airway disease or coronary artery disease.

Several motivations and concerns differed among patients who were and were not willing to participate in the hypothetical randomized controlled trial. For example, patients who were willing to participate cited personal health benefit as a motivating factor nearly twice as commonly as those unwilling to participate (Table 3). Shorter treatment time, need for fewer medications, and altruism were also cited more often by those willing to participate. In contrast, patients unwilling to participate were twice as likely to cite the inconvenience of coming 6 days as a concern as those willing to participate. Many patients stated concerns such as "[daily dialysis] would interfere with work," "when would I take care of my other medical appointments [on daily dialysis]?," "it is stressful to come after a full day of work; a lot of my strength is gone after [a] dialysis [treatment]."

Some patients stated concerns about social isolation with daily dialysis. "I could never do anything with my wife," "I spend weekends visiting my grandchildren," "I will not be able to spend time with my family." Others voiced concerns about their vascular access with daily dialysis. "My access infiltrates when I get stuck on 2 days back to back," "sometimes it takes 48 hours for the needle site to heal," "I have poor veins," "[daily dialysis] would blow my graft." However, there were no differences between patients who would or would not participate in the randomized controlled trial in the proportions of patients citing social isolation or fear of side effects (i.e., loss/damage to vascular access) as concerns (Table 4).

**Table 3.** Responses to question regarding randomized controlled trial of daily dialysis: What things would make participating appeal to you number (%)?

| | All patients | Not willing to participate | Willing to participate |
|---|---|---|---|
| | ($N = 209$) | ($N = 124$) | ($N = 85$) |
| Personal health benefit | 77 (37%) | 33 (27%) | 44 (52%)[a] |
| Other benefits: shorter treatment, etc. | 89 (43%) | 44 (36%) | 45 (53%)[a] |
| Fewer medications | 25 (12%) | 10 (8%) | 15 (18%)[b] |
| Altruism | 11 (5%) | 1 (1%) | 10 (12%)[a] |
| Contribute to knowledge | 5 (2%) | 2 (2%) | 3 (4%) |
| Better access to care | 2 (1%) | 0 (0%) | 2 (2%) |

[a]$P < 0.0001$, comparing those not willing to participate versus those willing to participate; [b]$P < 0.05$, comparing those not willing to participate versus those willing to participate.

Older patients, defined as age older than 56 years, had similar motivating factors as those patients younger than 56 years old. However, older patients were more likely to state no motivating factors than younger patients (51% versus 31%, $P < 0.01$). These older patients were also more likely to cite the inconvenience of coming 6 days a week for dialysis than younger patients (72% versus 54%, $P < 0.01$).

Patients with comorbid conditions such as history of coronary artery disease or reactive airway disease had similar motivating factors as those patients without these cormobidities. However, patients with these comorbidities were more likely to state no motivating factors than patients without these comorbidities (56% versus 35%, $P < 0.01$). These patients with comorbities were also

**Table 4.** Responses to question regarding randomized controlled trial of daily dialysis: What things concern you about participating number (%)?

| | All patients | Not willing to participate | Willing to participate |
|---|---|---|---|
| | ($N = 209$) | ($N = 124$) | ($N = 85$) |
| Inconvenience of coming 6 days | 132 (63%) | 102 (83%) | 30 (35%)[a] |
| Other concerns: Social isolation, etc. | 76 (36%) | 50 (40%) | 26 (31%) |
| Fear of side effects | 64 (31%) | 33 (27%) | 31 (36%) |
| Skeptical of research | 1 (1%) | 0 (0%) | 1 (1%) |
| Effect on other illness | 3 (1%) | 1 (1%) | 2 (2%) |

[a] $P < 0.0001$, comparing those not willing to participate versus those willing to participate.

more likely to cite the inconvenience of coming 6 days a week for dialysis than patients without these comorbidities (78% versus 57%, $P < 0.01$).

### Influence of teaching on willingness to participate

Of the original 209 patients, 177 (85%) agreed to and were available for the second interview. The remaining 32 were lost due to death (6), transfer to another dialysis unit (7), hospitalization (6), transplantation (5), or refusal to be interviewed again (8). Overall, the percentages of patients who said they "definitely would not," "probably would not," "maybe would not," "maybe would," "probably would," and "definitely would" participate were now 41%, 19%, 5%, 14%, 10%, and 11%, respectively. Thus, 35% of the 177 surveyed patients said they were willing to participate in an randomized controlled trial of daily dialysis after extensive teaching about the regimen's potential benefits (Fig. 2). Within patients, there was no appreciable change in willingness to participate between the preteaching and postteaching assessments (McNemar's chi-square = 2.19, $P = 0.14$). However, in the postteaching assessment, there was a polarizing effect toward more responses being "definitely yes" or "definitely no" (Fig. 2). Those who could not be surveyed for the postteaching assessment did not differ from those who completed both assessments in their distributions of age, gender, race, education, income or baseline willingness to participate (data not shown). Although our study was not specifically powered to detect such differences, these null findings suggest that the analyses of the influence of teaching on willingness to participate are not biased by a selected group of individuals not being available for the second assessment.

## DISCUSSION

We found that 41% of 209 patients who agreed to be interviewed at our inner city and suburban dialysis centers indicated a willingness to participate in a hypothetical trial comparing conventional with daily dialysis (Fig. 2). To the extent that this stated willingness to participate predicts the actual enrollment decisions patients would make [23], this result suggests that the majority of ESRD patients may not agree to enroll in upcoming randomized controlled trials.

Most of the patients in our sample who would participate in the randomized controlled trial cited the potential for personal health benefits. Potential health benefits have been cited as common motivations among patients considering enrollment in cancer and cardiovascular treatment trials [24–27]. However, a recent systematic review suggested that across all diseases, altruism is the most commonly cited motivation for participating in randomized controlled trials [16]. Altruism appears to be a particularly common motivation among human immunodeficiency virus (HIV)-infected patients [28] and those at high risk for HIV infection [29]. Thus, our results suggest that patients with ESRD may be similar in their enrollment preferences to patients with other noninfectious chronic diseases.

In order to gain insight into the factors governing ESRD patients' decisions, we compared the motivations and concerns among patients who were and were not willing to participate in the trial. We found that patients who were willing to participate were almost twice as likely to point to primary personal health benefits as a motivating factor in their decision to participate. These patients were also more likely to cite other personal benefits such as shorter treatment time and the need for fewer medications (Table 3).

On the other hand, we found that a substantial proportion of ESRD patients would not participate because of the inconvenience of coming to dialysis 6 days a week. Inconvenience of coming to the unit was cited twice as commonly among those who said they would not participate as among those who said they would participate, despite there being no difference between these groups in their mode of transportation or length of time spent in transit for each session. Inconveniences of daily dialysis was cited more often by older patients and patients with comorbid conditions such as coronary artery disease or reactive airway disease than by younger patients and patients without these comorbidities. Concerns about the inconveniences of daily dialysis were also noted by patients undergoing daily dialysis in small pilot studies [8].

Nearly one third of patients were concerned about the possibility of side effects from daily dialysis, particularly the possibility that more frequent treatments would more quickly damage their access sites. We suggest that pilot studies of daily dialysis focus on the effects on the vascular access site; if such studies do not show significantly increased risks to access patency, relaying this information to patients may help augment participation in upcoming randomized controlled trials.

To estimate the generalizability of results of upcoming randomized controlled trials of daily dialysis, we investigated whether certain patient subgroups were more or less willing to become part of these trials' samples. First, we found that patients on the waiting list for kidney transplantation were less likely to participate. This may be attributable to these patients' reluctance to alter their care in the hopes of soon receiving a treatment with better life expectancy and quality of life.

Second, we found that in general, patients with fewer comorbidities were more willing to participate. Patients willing to participate were younger, more likely not to smoke, and less likely to have a history of reactive airway disease, or coronary artery disease. We might have expected the sicker patients to be more willing to participate in the trial in the hopes of receiving an intervention that would be more effective in reducing their mortality. Such considerations may explain why acutely ill patients who were hospitalized in the preceding 12 months were more willing to participate. However, the present observations suggest patients with more chronic comorbid illnesses may perceive that they are more burdened by their disease, and thus less able to accommodate changes to their treatment regimen.

Regardless of the basis for differences in willingness to participate between more and less ill patients, the existence of these differences suggests that several patient sub-groups, such as those who are older, who smoke, or who have cardiac disease, may need to be specifically targeted to ensure that upcoming trials of daily dialysis are generalizable to most ESRD patients. Further efforts to understand the factors that would motivate or deter participation among these subgroups could aid in augmenting recruitment.

Our study has at least three limitations. First, 18% of recruited ESRD patients refused to be surveyed. To protect the confidentiality of those unwilling to be interviewed, we did not explore ways in which these patients may have differed from the 82% who were willing to be interviewed. If differences exist, and if these differences are strongly associated with willingness to participate, this could have biased our estimate of the proportion of patients willing to participate in a future trial. Assuming that the 18% who refused to be surveyed would also refuse to participate in a randomized controlled trial of daily dialysis, only 32% of eligible patients would have been potentially willing to participate in such a trial.

A second limitation of this study is that our patients were predominantly African American. Among previous studies evaluating patients' preferences for trial enrollment, some have found that African American patients are less willing to participate than other patients [23]. whereas other studies have found no association between race and willingness to participate [25]. Lower willingness to participate among some groups of African American patients has been attributed to distrust of the medical profession. Among our sample, however, distrust of researchers or of research in general was rarely cited as a concern. Thus, we see no reason to assume that higher rates of willingess to participate will be found among samples with different racial compositions, but we cannot rule out this possibility.

Finally, we evaluated patients' stated willingness to participate in an upcoming trial so as to help guide design and recruitment of this trial, but we cannot be sure that those who say they would or would not participate would make similar decisions when actually faced with this choice. Earlier work suggests that among patients at high risk for HIV infection stated willingness to participate is the single best predictor of who will and will not ultimately enroll in real trials [23]. However, stated willingness to participate is an imperfect surrogate for enrollment, and understanding its predictive properties among patients with ESRD will require future investigations once actual trials are initiated.

## CONCLUSION

This study represents the first investigation of the willingness of ESRD patients to participate in a trial comparing conventional to daily dialysis. Our findings have many implications for the planned randomized controlled trials of daily dialysis. First, our results suggest that less than half of ESRD patients who are recruited will ultimately participate in such an randomized controlled trial. This suggests that many dialysis centers would have to be involved to ensure adequate enrollment. Second, because our teaching intervention failed to improve enthusiasm for trial participation, investigators cannot assume that simply informing patients of the potential benefits of daily dialysis will improve enrollment. Rather, investigators will need to develop novel approaches to address patients' concerns. Investigators will also need to address patients' concerns regarding the inconveniences of coming 6 days a week for dialysis on an individual basis. Future investigations should also assess patients' willingness to participate in trials of daily dialysis where the study design is modified. For example, it is not known if a run-in period of daily dialysis would allow patients to experience some of the short-term benefits of daily dialysis and thereby improve subsequent enrollment. Finally, in order to ensure generalizability to most ESRD patients, investigators might explore ways to target sub-groups of patients (i.e., older patients and those with coronary artery disease) who may be otherwise underrepresented.

## ACKNOWLEDGMENTS

A.K.I. has been supported by NIH F32 DK60298-01 and NIH K23 DK60298-01 grant. This project has been supported by a University of

Pennsylvania Research Foundation grant to A.K.I. and J.S.B. Special thanks to Hatem Amer, M.D., for his assistance with interviewing the dialysis patients. Part of this research was presented at the 2002 American Society of Nephrology meeting in Philadelphia.

*Reprint requests to Ajay K. Israni, M.D., Center for Clinical Epidemiology & Biostatistics, 102 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104.*
*E-mail: aisrani@cceb.med.upenn.edu*

## APPENDIX 1: DESCRIPTION OF HYPOTHETICAL TRIAL (TO BE READ TO EACH PATIENT)

### Research Study of Six Times a Week, In-Center Hemodialysis

Researchers at the University of Pennsylvania are planning to study a new dialysis schedule to treat kidney failure. Patients using this new schedule would receive their regular dialysis treatment six times each week, with each treatment lasting for 2 hours.

Some patients have previously been tested in smaller studies of six times a week dialysis. In these early studies, there did not appear to be any risks to having dialysis six times each week. The more frequent treatments did appear to have several benefits for patients. These patients had better blood pressures with the use of fewer medications, better blood counts with use of less medicines, and better results of other routine blood tests, including phosphate and calcium levels.

Most patients also felt better when getting six times a week dialysis treatments. For example, these patients had less cramps and nausea. However, we are not sure that all patients will have these benefits. It is also possible that getting dialysis six times each week may increase the chance that patients would need to have a procedure to repair the site at which they are hooked up to the dialysis machine.

To further study the risks and benefits of having dialysis treatments six times each week, researchers need 2000 patients like yourself to participate in a larger study comparing six times a week dialysis with three times a week dialysis. This study will last 3 years.

During the 3-year study, half of the study patients will continue their regular three times a week dialysis, and the other half will be changed to six times a week dialysis. Whether you receive six times a week dialysis or continue your regular three times a week dialysis will be determined by chance, like flipping a coin. Neither patients nor their doctors will get to choose whether they receive dialysis three or six times each week. Those patients assigned to receive dialysis six times a week would go to their regular dialysis units every day of the week except Sunday, to be treated for 2 hours each day. Patients would not be charged for any of these treatments.

If the six times a week hemodialysis is shown to be safe and effective, you and other people needing dialysis might be able to receive six times a week dialysis as treatment in the future.

### Questions Assessing Patients' Understanding of the Trial

1. Can you tell me how it will be decided which patients in this study get three times a week dialysis and which will get six times a week dialysis?
2. If you are assigned to receive dialysis six times a week, would each treatment last for longer, shorter, or about the same amount of time as the treatments you currently get three times each week?
3. How long will this study last?
4. Do you have any questions about what the study?

### Open-Ended Questions About Factors Influencing Enrollment Decisions

1. In thinking about this study, what things would make participating appeal to you?
2. In thinking about this study, what things concern you about participating?

### Question Assessing Willingness to Participate

1. How willing would you be to participate in this study of six versus three times a week dialysis? Please answer with one of the following six levels of willingness: "I would definitely not participate," "I would probably not participate," "I might not participate," "I might participate," "I probably would participate," or "I definitely would participate."

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| Definitely Not | Probably Not | Might Not | Might | Probably | Definitely |

## APPENDIX 2: DESCRIPTION OF TEACHING SESSION (TO BE READ TO EACH PATIENT)

### Daily Dialysis Teaching

In 1970s regular dialysis was started to save lives of people with kidney disease like yourself. Hemodialysis has generally been done three times a week. Clearly, dialysis done this way has greatly benefited patients with kidney failure, improving their life expectancy, and quality of life.

Recently, it has been suggested that dialysis done more than three times a week may be even better for dialysis patients.

What is daily dialysis? It is like your regular dialysis but with shorter treatment of only 2 hours but done 6 days a week (all days except Sunday), rather than your usual three times a week treatments for 3 to 4 hours.

Daily dialysis has been tried in small groups of patients in the United States, Canada, and Europe.

The more frequent treatments appear to benefit patients. We will now describe these potential benefits:

Daily dialysis may be better for controlling your blood pressure: (*1*) it may lead to better blood pressure control; (*2*) fewer medicines may be needed for high blood pressure; and (*3*) better blood pressure control causes less stress on the heart and less heart disease

Keep in mind that heart disease is the number one killer in dialysis patients. Daily Dialysis may improve your red blood count: (*1*) it may lead to higher red blood count; and (*2*) higher blood count causes less stress on the heart, less heart disease, better energy level, and better ability to be active and do execise

Daily dialysis may allow you to have fewer restrictions in your diet. With daily dialysis: (*1*) patients can eat more of the foods they like; and (*2*) patients can drink more of the things they like.

Daily dialysis may cut down on the need for medicines: (*1*) fewer medicines may be needed to treat high blood pressure; (*2*) some might be able to stop these high blood pressure medicines altogether; and (*3*) fewer medicines may be needed to control the phosphorous level.

Daily dialysis may make you feel better: (*1*) less cramps on daily dialysis; (*2*) less nausea on daily dialysis; and (*3*) patients seem to feel their best more often on daily dialysis than with regular three times a week dialysis.

Daily dialysis may reduce need for hospital admissions. In the long-run, daily dialysis may reduce the need for hospital admission, reduce the number of days needed in the hospital, and increase the chance of living longer.

So far, daily dialysis has been safe, with no harmful side effects. Patients in Europe and Canada who have received daily dialysis have not needed extra procedures to repair the site at which they are hooked up to the dialysis machine. However, only a few patients have received daily dialysis so far. It is possible that daily dialysis may increase the chance that patients would need to have a procedure to repair the site at which they are hooked up to the dialysis machine (your shunt, fistula, or graft) [pointing to patient's access site].

To further study the risks and benefits of daily dialysis, we are planning a research study of daily dialysis. This study will last 3 years and allow 2000 patients like yourself from all over the country to participate.

During the 3 years of the study, one half the patients will continue their regular three times a week dialysis for the usual length of time, and the other half will be changed to six times a week daily dialysis for 2 hours as we discussed earlier. Neither patients nor their doctors will get to choose whether they receive dialysis three or six times each week. It will be determined by chance, like flipping a coin.

If you decide to participate in the study of daily dialysis, you would not be charged for these dialysis treatments. We would pay for your ride to and from the dialysis unit

If six times a week daily dialysis is shown to be safe and effective, you and other people needing dialysis might be able to receive six times a week dialysis as treatment in the future.

We would allow you to participate in the study of daily dialysis only if your doctor agrees that it is safe for you.

## REFERENCES


1. Depner T: Why daily hemodialysis is better: Solute kinetics. *Semin Dial* 12:462–471, 1999
2. RPA/ASN Position on Daily Dialysis: Task Force on Daily Dialysis, Bethesda, MD, National Institutes of Health, NIDDK, 2001
3. Woods J, Port F, Orzol S, *et al*: Clinical and biochemical correlates of starting "daily" hemodialysis. *Kidney Int* 55:2467–2476, 1999
4. Traeger J, Sibai-Galland R, Delawari E, *et al*: Daily versus standard hemodialysis: One year experience. *Artif Organs* 22:558–563, 1998
5. Ting G: Future role of short daily hemodialysis, an opinion based on a California study. *Nephrol Dial Transplant* 12:448–450, 1999
6. Buoncristiani U, Qunitaliani G, Cozzari M, *et al*: Daily dialysis: Long-term clinical metabolic results. *Kidney Int* 33 (Suppl 24):S137–S140, 1988
7. Buoncristiani U: Fifteen years of clinical experience with daily haemodialysis. *Nephrol Dial Transplant* 13:S148–S151, 1998
8. Mohr P, Neumann P, Franco S, *et al*: The case for daily dialysis: Its impact on costs and quality of life. *Am J Kidney Dis* 37:777–789, 2001
9. United States Renal Data System: USRDS Annual Data Report, Bethesda, MD, National Institutes of Health, NIDDK, 2002
10. Anonymous: NIH seeking applications. *Nephrol News Issues* February:30–31, 2003
11. National Institute of Diabetes Digestive and Kidney Diseases (NIDDK): RFA DK-03–005, in *Frequent Hemodialysis Clinical Trials*, Bethesda, National Institutes of Health, 2002
12. Halpern SD, Karlawish JHT, Berlin JA: The continuing unethical conduct of underpowered clinical trials. *JAMA* 288:358–362, 2002
13. Halpern S: Prospective preference assessment: A method to enhance the ethics and efficiency of randomized controlled trials. *Controlled Clinical Trials* 23:274–288, 2002
14. Lovato LC, Hill K, Hertert S, *et al*: Recruitment for controlled clinical trials: Literature summary and annotated bibliography. *Controlled Clinical Trials* 18:328–352, 1997
15. Hunningshake DB, Darby CA, Probstfield JL: Recruitment experience in clinical trials: Literature summary and annotated bibliography. *Controlled Clinical Trials* 8:6S–30S, 1987
16. Ross S, Grant A, Counsell C, *et al*: Barriers to participation in randomised controlled trials: A systematic review. *J Clin Epidemiol* 52:1143–1156, 1999
17. Silverman WA, Altman DG: Patients' preferences and randomised trials. *Lancet* 347:171–174, 1996
18. Feinstein AR: An additional basic science for clinical medicine. II. The limitations of randomized trials. *Ann Intern Med* 99:544–550, 1983
19. Greene T: Trial design issues—Outcome and sample size, in *Task Force on Daily Dialysis*, Bethesda, MD, National Institutes of Health, NIDDK, 2001, pp 31–32
20. Andre M, Rembold S, Pereira C, *et al*: Prospective evaluation of an in-center daily dialysis hemodialysis program: Results of two years of treatment. *Am J Nephrol* 22:473–479, 2002
21. Galland R, Traeger J, Arkouche W, *et al*: Short daily hemodialysis rapidly improves nutritional status in hemodialysis patients. *Kidney Int* 60:1555–1560, 2001
22. Mohr P: The economics of daily dialysis. *Adv Renal Replace Ther* 8:273–279, 2001
23. Halpern S, Metzger D, Berlin J, *et al*: Who will enroll? Predicting participation in a phase II AIDS vaccine trial. *J Acquir Immune Defic Syndr* 27:281–288, 2001
24. Cassileth BR, Lusk EJ, Miller DS, *et al*: Attitudes toward clinical trials among patients and the public. *JAMA* 248:968–970, 1982
25. Halpern SD, Karlawish JHT, Casarett D, *et al*: Hypertensive patients' willingness to participate in placebo-controlled trials: Implications for recruitment efficiency. *Am Heart J* (in press)
26. Roberson NL: Clinical trial participation: Viewpoints from racial/ethnic groups. *Cancer* 74:2687–2691, 1994
27. Sugarman J, Kass NE, Goodman SN, *et al*: What patients say about medical research. *IRB: A Review of Human Subjects Research* 20:1–7, 1998
28. Ross MW, Jeffords K, Gold J: Reasons for entry into and understanding of HIV/AIDS clinical trials: a preliminary study. *AIDS Care* 6:77–82, 1993
29. Koblin BA, Avrett S, Taylor PE, *et al*: Willingness to participate in HIV-1 vaccine efficacy trials and the effect of media events among gay and bisexual men in New York City: Project ACHIEVE. *J Acquir Immune Defic Syndr Hum Retrovirol* 15:165–171, 1997